UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: January 23, 2014

SUBJECT: Sulfuryl Fluoride: Summary of Hazard and Science Policy Council (HASPOC) Meeting of September 12, 2013: Recommendations on the Requirement of a Developmental Neurotoxicity Study.

PC Code: 078003
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056796
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

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THROUGH: Jess Rowland, Co-Chair
Anna Lowit, Ph.D., Co-Chair
HASPOC
Health Effects Division (7509P)

TO: PV Shah, Branch Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)
and
Christina Swartz, Branch Chief
Risk Assessment Branch II (RAB2)
Health Effects Division (7509P)

MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Kristin Rury, Jeff Dawson, Jess Rowland, Jonathan Chen, Julie VanAlstine, Michael Metzger, PV Shah

Presenter: Elizabeth Holman

Other Attendees: Christina Swartz, Jaime D'Agostino, Jack Housenger, Linda Taylor, and the following representative from the California Department of Pesticide Regulation: Dave Rice, Gary Patterson, Jag Snyder, Paul Kelner, Paul Moore, Peter Leong

I. PURPOSE OF MEETING:

In May 2009, the Health Effects Division (HED) issued a human health Registration Review scoping document (D359667) for the fumigant sulfuryl fluoride (SF). In this document, it states that: "*In April 2004, the Health Effects Division granted a waiver for the Developmental Neurotoxicity (DNT) study based on the lack of chronic dietary exposure, minimal short-term exposure, animal welfare concerns, and a rat metabolism study which shows that SF is rapidly metabolized to fluoride. However, there remains uncertainty in the absence of a DNT; therefore, EPA has retained the FQPA 10X factor in assessing the risk posed by SF. Recent advances in study technique have made inhalation DNTs appropriate for endpoint consideration (e.g. methyl bromide); therefore, HED is requesting that an inhalation DNT be completed for sulfuryl fluor*ide".

In July, 2011, the Registrant, Dow AgroSciences LLC, Indianapolis, provided their rationale for the removal of the database uncertainty factor as well as requested a waiver of the DNT (MRID 48549214). In addition, the Registrant submitted pharmacokinetic studies and the results (no input parameters for the models) of physiological based pharmacokinetic (PBPK) modeling analysis to support a waiver for the required DNT study by the inhalation route. These studies (MRID 48549201-48549213) were reviewed by HED and data evaluation records (DERs) have been prepared.

In July 2012, two other Registrants, Drexel Chemical Company, Memphis, TN and Ensystex II, Inc. of Fayetteville, NC, jointly submitted a waiver request for a DNT study (MRID 48896102).

The HASPOC met on September 12, 2013 to discuss the need for a DNT study by the inhalation route for SF in light of the newly submitted pharmacokinetics and modeling data along with existing 40 CFR Part 158 toxicity data.

II. RATIONALE FOR DEVELOPMENTAL NEUROTOXICITY STUDY**:**

In a 2003, the Hazard Identification Assessment Review Committee (HIARC) required a DNT for SF based on the following considerations (TXR No. 0052208):

> "In numerous subchronic and chronic inhalation toxicity studies on rats, mice, dogs, and rabbits, a treatment-related neurotoxic lesion described as malacia (necrosis) and/or as vacuolation of the white fiber tracts in the brain was regularly reported at dose levels as low as 90 mg/kg/day in a 2-week study in rabbits, at dose levels as low as 28 mg/kg/day in a 90-day study in rabbits, at dose levels as low as 50 mg/kg/day in a 90-day study in dogs, at dose levels as low as 50 mg/kg/day in a 1-year study in dogs, and at dose levels

as low as 56 mg/kg/day in a 2-year study in rats. In these studies, clinical signs of neurotoxicity (e.g. tremors, tetany, in coordination, excessive salvation) were sometimes observed at dose levels below those at which malacia and/or vacuolation was observed in the brain, sometimes at higher dose levels, and sometimes not at all at any of the dose levels tested. In a specially designed 90-day neurotoxicity study in rats, disturbances in electrophysiological waveforms (EEG patterns) were observed at a dose level (80 mg/kg/day) lower than the dose level at which malacia/vacuolation was observed in the brain (240 mg/kg/day). The parts of the brain in which these lesions were present were frequently the caudate-putamen nucleus in the basal ganglia of the cerebrum, and the white fiber tracts of the internal and external capsules and globus pallidus of the cerebrum".

III. WEIGHT OF THE EVIDENCE (WOE) APPROACH

In accordance with the 40 CFR Part 158 Toxicology Data Requirements, the DNT is "conditionally required" based on weight of evidence (WOE) considerations. In the case of SF, the following bullets provide short summaries of the data which was provided to HASPOC for consideration of the DNT waiver:

- *In vitro*, hydrolysis of SF in blood was similar between adult rat blood and PND 10 rat pup blood, but it was approximately two fold less than human blood (MRID 48549203). This indicates that there is no difference in the metabolism of SF between adult and rat pups, and that rats are less sensitive than humans.

- The results of the *in vitro* studies suggest that blood within the local respiratory tissues is important for hydrolysis of SF. Aliquots of nasal lavage fluid (NLF) and bronchoalveolar lavage fluid (BALF) and whole blood were processed for quantitation of SF within 10 minutes of the end of exposure. No parent SF was detected in any blood or lavage sample which indicates that the parent molecule was rapidly hydrolyzed at the portal of entry and was not present systemically thus resulting in no exposure to SF *per se* (MRID 48549206).

- In rats, absorbed SF was rapidly excreted in the urine and feces. Urine contained greater 85.6% of the total excreted radioactivity and most of the excretion occurred in first 24 hours. The major component in the feces was identified as the parent compound representing 91-93% the total fecal excretion (<10% of the dose) in rats, indicating rapid metabolism and no bioaccumulation (MRID 48549204).

- *In vitro*, SF is rapidly hydrolyzed to fluorosulfate (FO_3S) and fluoride ion (F). However, further hydrolysis of fluorosulfate to sulfate (SO_4) and additional F is a relatively slow process (MRID 48549214).

- Metabolism studies were conducted in rats, rabbits, and PND22 rat pups. These studies demonstrated that the SF was rapidly absorbed and excreted from the body following inhalation exposure in rats, rabbits, and PND 22 rat pups indicating no species-specific differences in the handling of SF (MRID 48549209 and 48549210).

- No differences in plasma elimination half-lives were observed when rats were exposed to SF at 300 ppm following a single exposure or following 10 days of repeated exposure, indicating no bioaccumulation and a lack of cumulative toxicity (MRID 48549208).

- The plasma kinetics in adult rats and PND 22 rats were similar following inhalation exposure at doses up to 300 ppm. No differences in residue levels of fluorosulfate and fluoride were observed between PND 22 and adult rats (MRID 48549210).

- The plasma net free F concentration was consistently higher (3X) in rabbit plasma compared to rat plasma (MRID 48549212).

- During gestation, fetal plasma levels of FO_3S were markedly lower (8X) than dam plasma FO_3S levels at 5-150 ppm SF after 6 hours of exposure. During lactation, pup plasma FO_3S and free F levels were lower than (6X) dam levels despite 2-5X higher levels of FO_3S and free F in milk relative to maternal plasma. This indicates lower internal doses of FO_3S and F in pups or fetuses compared to maternal levels (MRID 48549209).

- No evidence of increased susceptibility was seen in both the developmental toxicity studies in rats and rabbits and in a 2-generation reproduction study in rats conducted via the inhalation route of exposure. In the 2-generation reproduction study in rats, the histopathological findings (vacuolation of caudate putamen tracts in brain) were observed in the parent animals but not in F1 or F2 adults. No clinical signs of neurotoxicity were observed in pups. However, neurobehavioral parameters were not evaluated in the reproductions study, therefore, there is uncertainty for neurobehavioral effects in the developing offspring, particularly following inhalation exposure.

- No evidence of neurotoxicity was observed in the acute neurotoxicity study in rats; however, neuropathological examinations were not performed in the study as per agreed protocol. In a subchronic neurotoxicity study in rats via the inhalation route, vacuolation of white matter in caudate putamen in cerebrum was observed at the high dose of 300 ppm.

- The available pharmacokinetic data shows that there is a limited exposure to SF since it is rapidly metabolized to FO_3S and F. Therefore, it is presumed that the neurotoxicity seen in the toxicity studies with SF are due to fluoride and not due *per se* to SF. A number of neurotoxicity studies and a DNT are available for fluoride. In these studies, however, the animals were exposed to fluoride *via* drinking water. The toxicity studies, including the DNT conducted for fluoride *via* the oral route (drinking water) may not be relevant for human health risk assessment because the physiological concentrations may not be similar between oral (drinking water) and inhalation routes of exposure. The available data suggests that SF is rapidly metabolized to FO_3S and F and the metabolism rate is species-dependent. Based on this data it can also be concluded that the toxic moiety is F that results in neurotoxicity.

i. Species Sensitivity Relevant to Humans (Rat vs Rabbit)

The comparative pharmacokinetic studies between rats and rabbits clearly suggest that pharmacokinetic data in rabbits were consistent with the extensive SF pharmacokinetic data in rats. However, the conversion of fluorosulfate to fluoride in rabbits is 3X faster in rabbits than in rats. Available data clearly suggest that human blood hydrolysis of SF is 2X faster than rat blood (Adult as well as PND 10 rat). Based on this information, the sensitivity of humans could be between the sensitivity of rats and rabbits in terms of hydrolysis of SF. Available pharmacokinetic data indicate no significant accumulation of SF and/or its metabolites in tissues. The neurotoxic effects seen in SF studies are presumed to be due to free fluoride. Therefore, because the rabbit is the most appropriate species for risk assessment, a DNT in rats would be of little value. No data are available to conclude that the hydrolysis of SF is similar in adult and neonatal rabbits.

ii. Data on Lifestage Sensitivity

Available data on SF demonstrate that there are no uncertainties regarding in utero exposure. The developmental toxicity studies in rats and rabbits via inhalation route of exposure do not indicate susceptibility of fetuses to SF exposure. There was no evidence of increased susceptibility from pre and post-natal exposure to SF in the two generation reproduction study in rats via inhalation. However, the potential susceptibility of young following post-natal exposure is not fully characterized because some of neuro development parameters are routinely not evaluated in the two generation reproduction study.

There are special studies conducted to characterize potential post-natal susceptibility following exposure to SF. No difference was observed in the rate of in vitro hydrolysis of SF to fluorosulfate between adult rat and PND 10 rat pup blood. Several pharmacokinetics studies do not suggest any difference in pharmacokinetic parameters of inhaled SF by adult and PND 21 rat pups. Studies in PND 10 rat pup via gavage route of exposure demonstrate detectable levels of fluoride in the brain tissue and the peak F levels in the cerebrum also were roughly proportionate to exposure concentrations. The comparative pharmacokinetics studies between adult rats and pups were conducted via different routes of exposure (inhalation vs oral gavage). In addition, pups were not directly exposed to SF from PND 10 to PND 21, so a critical developmental period might have been missed. There are no other data are available to address this concern and therefore, some residual uncertainties remain regarding post-natal exposure.

The rabbit appears to be most sensitive species to SF exposure. Although there is no evidence for increased susceptibility in the pre-natal developmental toxicity study in rabbits, brains of fetuses, a key target for SF-induced toxicity, were not evaluated in the pre-natal developmental toxicity study. In addition, there is still uncertainty due to the absence of data in the early post-natal life stage where there are rapid changes in the brain of rabbits following inhalation exposure.

IV. HASPOC RECOMMENDATIONS

The HASPOC concludes that since the available data clearly show that rabbits are more sensitive than rats to SF, conducting a DNT with rats would not provide useful information. Additionally, the results obtained from the pharmacokinetic studies clearly show that there is still uncertainty regarding the potential toxicity to the developing brain from pre-and post natal exposure to SF in rabbits, the most sensitive species.

The HASPOC concluded that additional studies would be required to address these concerns in rabbits. Therefore, the HASPOC recommends that the Registrant(s) begin a dialogue with the Agency to determine the appropriate study(ies) that would address the concerns discussed above. In this endeavor, the Agency suggests that one potential study to be conducted may be an in vitro comparative hydrolysis rate of SF with adult and developing rabbit pups to ascertain that the rate of hydrolysis of SF to fluorosulfate and fluoride is similar between adult vs. young. Another suggested study for consideration is a comparative pharmacokinetic study in adult and developing rabbit pups via inhalation route of exposure. In the absence of these additional studies, a 10X database uncertainty factor will be required for all routes of SF risk assessment.